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18-MC reduces methamphetamine and nicotine self-administration in rats

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In previous studies, 18-methoxycoronaridine (18-MC), a novel *iboga* alkaloid congener, has been found to decrease the intravenous self-administration of morphine and cocaine in rats. In the present study, 18-MC (1–40 mg/kg, i.p.) dose-dependently decreased the i.v. self-administration of methamphetamine and nicotine. As in the previous studies, drug self-administration was reduced for ≥ 24 h after the highest dose

of 18-MC. A comparison of 18-MC's interactions with all four drugs of abuse studied so far indicated that 18-MC is least effective in decreasing methamphetamine self-administration and most potent in decreasing nicotine self-administration. The results suggest that a nicotinic antagonist action of 18-MC contributes to its putative anti-addictive efficacy. *NeuroReport* 11:2013–2015 © 2000 Lippincott Williams & Wilkins.

Key words: Addiction; Drug self-administration; Ibogaine; Methamphetamine; 18-Methoxycoronaridine; Nicotine

INTRODUCTION

18-Methoxycoronaridine (18-MC) is a synthetic analogue of ibogaine, an alkaloid found in the root bark of the African shrub *Tabernanthe iboga*. Based on anecdotal reports in humans, ibogaine has been claimed [1] to be effective in interrupting dependence on opioids, stimulants, alcohol and nicotine. Preclinical studies in rats have supported these claims: ibogaine has been reported to decrease the i.v. self-administration of morphine [2] and cocaine [3] and the oral intake of alcohol [4] and nicotine [5]. However, studies in rats have also raised concerns regarding potential adverse effects of ibogaine; most notably, high doses have been shown to be neurotoxic to the cerebellum [6,7]. In view of such concerns, we began to collaborate with medicinal chemists (M.E. Kuehne and U. Bandarage) at the University of Vermont in an attempt to develop an ibogaine-like agent that would be safer than ibogaine yet retain its efficacy in drug self-administration models. After testing more than a dozen chemical entities, we identified 18-MC as the first *iboga* alkaloid congener likely to meet both safety and efficacy criteria [8].

Like ibogaine, 18-MC, at comparable doses, has been found to decrease the i.v. self-administration of morphine [8] and cocaine [8] and the oral intake of alcohol [9] and nicotine [5]. Unlike ibogaine, 18-MC does not produce whole body tremors [8], damage the cerebellum [8], decrease heart rate [10], or inhibit responding for a non-drug reinforcer (water) [8]. On some aspects of drug self-administration, 18-MC appears to have somewhat greater efficacy or potency than ibogaine. Thus 18-MC seems to have a longer-lasting effect than ibogaine on morphine self-administration [2,8] and to be approximately twice as potent as

ibogaine in attenuating oral nicotine preferences [5]. The latter finding was of particular interest in view of published reports [11,12] that ibogaine can act as a non-competitive nicotinic antagonist and that, in preliminary studies [10], 18-MC may have a similar action. Because different self-administration models (oral *vs* i.v.) were used, it was not clear whether or not 18-MC preferentially affected nicotine self-administration over the self-administration of other drugs. In the present study, in order to be able to better compare the interaction of 18-MC with nicotine to its interactions with other self-administered drugs, the effect of 18-MC on i.v. nicotine self-administration was assessed; and to further explore the generality of 18-MC's actions, the effect of 18-MC on i.v. methamphetamine self-administration was also assessed.

MATERIALS AND METHODS

Animals: Drug-naïve female Long-Evans derived rats (250 g; Charles River, NY) were maintained on a normal 12:12 h light:dark cycle (lights on at 07:00 h). For all experiments the Principles of Laboratory Animal Care (NIH publication No. 85-23, revised 1985) were followed.

Self-administration procedure: The i.v. self-administration procedure has been described previously [2,3,8]. Briefly, responses on either of two levers (mounted 15 cm apart on the front wall of each operant test cage) were recorded on an IBM compatible computer with a Med Associates, Inc. interface. The i.v. self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks (1972), Instech harnesses and swivels, and Harvard Apparatus infusion

pumps (55-2222). Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to procedures described by Weeks [13]. Self-administration testing began with a 16 h nocturnal session followed by daily 1 h sessions, 5 days (Monday–Friday) a week. A lever-press response produced a 50 μ l infusion of drug solution (0.01 mg nicotine hydrogen bitartrate or 0.025 mg methamphetamine sulfate) in about 1 s. Since all rats generally weighed 250 ± 20 g, each response delivered ~ 0.04 mg/kg (0.014 mg/kg free base) nicotine or 0.1 mg/kg methamphetamine.

Experiments to assess the effects of 18-MC on responding for nicotine and methamphetamine were begun when baseline self-administration rates stabilized, usually after 2 weeks of testing. All 18-MC or vehicle treatments were administered i.p. 15 min before testing on Wednesdays. Different doses of 18-MC (or vehicle) were administered to different groups of rats. All cannulas were tested with methohexital (immediate ataxia in response to 5 mg/kg) on Fridays and only the data from rats having patent cannulas were included in the analysis of effects.

Statistical analysis: The data, expressed as percentage of baseline infusions/h, were analyzed using analysis of variance (ANOVA) followed by paired *t*-tests for comparing 18-MC effects to baseline performance.

RESULTS

The average ($\pm$ s.e.m.) numbers of baseline responses (infusions) per hour for methamphetamine and nicotine were 19.1 ± 1.4 ($n = 45$ rats) and 28.3 ± 2.0 ($n = 47$ rats), respectively. Figure 1 shows the acute effects of 18-MC on methamphetamine and nicotine self-administration. 18-MC produced dose-related decreases in the self-administration of both drugs (ANOVA, $p < 0.0001$ in both cases). Subsequent comparisons (paired *t*-tests) between baseline and treatment days showed that 18-MC doses ≥ 10 mg/kg significantly ($p < 0.05$) decreased responding for methamphetamine while 18-MC at doses ≥ 2 mg/kg significantly ($p < 0.05$) decreased responding for nicotine. Figure 2 shows the after-effects of 18-MC, 40 mg/kg: 18-MC significantly ($p < 0.05$) decreased both methamphetamine and nicotine self-administration for ≥ 24 h (i.e. 18-MC was administered prior to testing on Day 1 and there were still significant effects on Day 2).

DISCUSSION

Similar to previous findings with morphine and cocaine [8], 18-MC (10–40 mg/kg) decreased methamphetamine self-administration and nicotine self-administration on the day of 18-MC treatment and, after 40 mg/kg, on the following day as well. However, some differences in 18-MC's interactions with these four drugs of abuse are apparent. 18-MC appears to be least effective in decreasing methamphetamine self-administration and most potent in decreasing nicotine self-administration. Thus while the highest dose (40 mg/kg) of 18-MC decreased morphine, cocaine and nicotine self-administration to $< 20\%$ of baseline, methamphetamine self-administration was only reduced to 40% of baseline. On the other hand, 5 mg/kg 18-MC reduced nicotine self-administration to 60% of base-

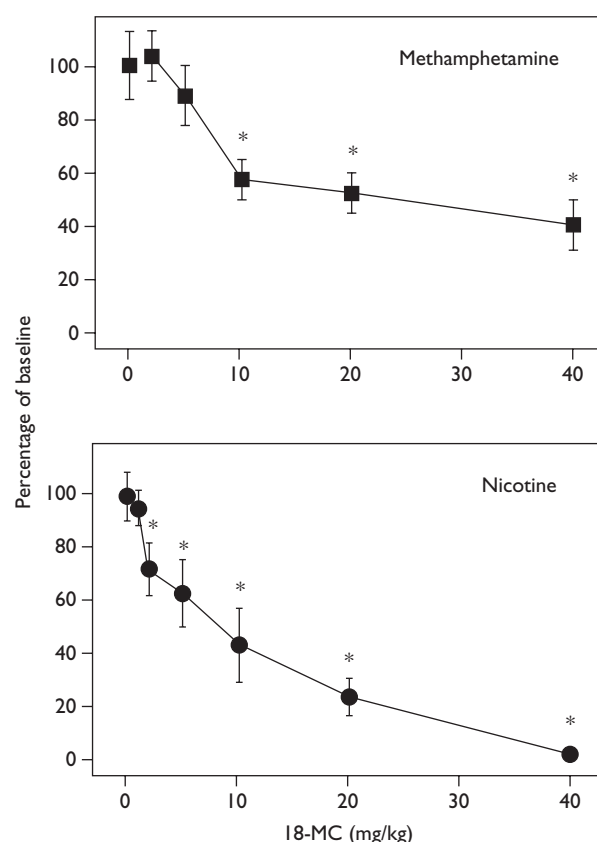


Fig. 1. Acute effects of 18-MC on methamphetamine and nicotine self-administration. Each data point is the mean ($\pm$ s.e.m.) from 6–9 rats. Baseline was calculated as the average rate for the two test sessions preceding drug or saline (0 mg/kg) treatment. * $p < 0.05$; treatment significantly different from baseline.

line, equivalent to the effects of 10 mg/kg 18-MC on morphine, cocaine and methamphetamine self-administration. Even 2 mg/kg 18-MC significantly decreased nicotine self-administration, a dose which had no effect on methamphetamine self-administration (present study) or on morphine or cocaine self-administration (unpublished data). These differences in 18-MC's drug interactions are not likely to be attributable to procedural or other non-specific factors: baseline rates of responding were similar in each case and the unit infusion doses of the self-administered drugs were all near the peaks of their dose-response functions; moreover, even 40 mg/kg 18-MC does not affect responding for water [8].

Although the present study does not directly address the issue of how 18-MC alters sensitivity to methamphetamine and nicotine, a recent study [14] showed that 18-MC produced a downward shift, without any displacement to the left or right, in the entire dose-response curve for self-administered morphine. This indicated that 18-MC reduced the reinforcing efficacy of morphine without altering its apparent potency. The similar nature of the interactions of 18-MC with other drugs suggests that their reinforcing efficacies are also reduced by 18-MC. This is especially likely for nicotine since both a nicotinic agonist and a

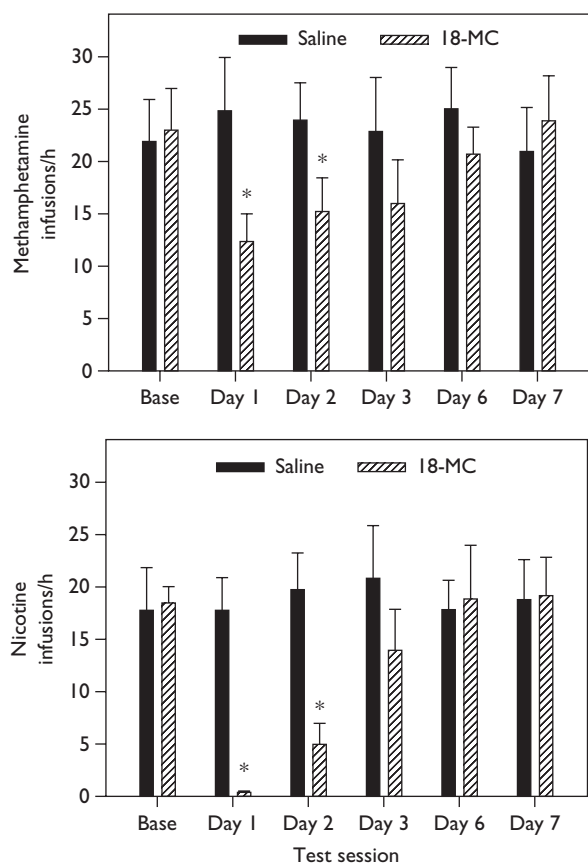


Fig. 2. After-effects of 18-MC (40 mg/kg) on methamphetamine and nicotine self-administration. Each data point is the mean ($\pm$ s.e.m.) from 6–8 rats. Base refers to the baseline rate of responding, calculated as the average for the two test sessions preceding drug or saline treatment. * $p < 0.05$, treatment significantly different from baseline.

nicotinic antagonist will decrease nicotine self-administration [15]. It should also be noted that 18-MC appears to be much more potent in decreasing i.v. self-administered nicotine than orally self-administered nicotine [5]; oral nicotine seems to have aversive as well as rewarding effects [16] and 18-MC might block both effects, resulting in no change in nicotine intake at low doses of 18-MC.

Although its precise mechanism of action is unknown, receptor binding studies have shown that 18-MC has low μ M affinities for mu, delta, and kappa opioid receptors and for 5-HT₃ receptors [10]; recent functional studies have shown it to act, at low micromolar concentrations, as an antagonist at α 3- β 4 nicotinic receptors (unpublished results; NIMH Psychoactive Drug Screening Program). The present results, indicating that 18-MC has some selectivity for nicotine self-administration *vs* the self-administration of other drugs, suggest that a nicotinic antagonist action of 18-MC contributes to its putative anti-addictive efficacy. However, the broad spectrum of 18-MCs activity is probably attributable to a combination of actions at multiple receptors.

CONCLUSION

18-MC, a novel *iboga* alkaloid congener, reduces intravenous methamphetamine and nicotine self-administration in rats. These and previous results with morphine, cocaine and alcohol indicate that 18-MC warrants further development as a potential treatment for multiple forms of drug addiction.

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